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HOPITAL D'INSTRUCTION DES ARMEES PERCY
HAEMATOLOGY DEPARTMENT

DISPATCH NOTE

Clamart, 19 November 2004
Nº 978/DEF/HIAPERCY/HEMATO/

DESIGNATION	NUMBER	OBSERVATIONS
Object: - Hospitalisation Record in the Haematology Department of: **Mr Yasser ARAFAT** - Stay from 29/10/04 to 03/11/04 **Attachments**: **1 – Hospitalisation report of 10 pages** **2 – Additional examinations:** - Haematology: 26 pages numbered from A1 to A26 - Haemostasis: 13 pages numbered from B1 to B13 - Biochemistry: 43 pages numbered from C1 to C43 - Infection and Autoimmunity: 53 pages numbered from D1 to D53 - Radiology and EEG: 6 pages numbered from G1 to G6 **3 – Nursing records and prescriptions**: - Nursing transmissions: 5 pages numbered from E1 to E5 - Examination prescriptions: F2 - Monitoring and treatment record: F1 – F3		**SENT FOR ALLOCATION** **Chief Doctor T de REVEL** **Head of Department** **Haematology Department** HIA PERCY – 92141 CLAMART Tel 01 41 46 63 01 – Fax 64 65 ADELI Code: 961014297

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Hopital d'Instruction des Armees PERCY Clamart, 14 November 2004

Haematology Department

HOSPITALISATION REPORT

Re: **Mr Yasser ARAFAT** born on 04/08/1929
Arrived on 29/10/2004 – Left on 03/11/2004
Referring doctors: Professor de Revel; Doctor Fagot

Reason for hospitalisation:

Exploration of thrombopaenia in a context of alteration of the general condition with digestive problems evolving over two weeks.

Personal and family history:

- Chronic subdural haematoma in 1990 treated surgically 6 months after an air crash
- Vitiligo
- Essential tremor treated with Avlocardyl 160 LP for 10 years, currently stabilised
- Gastritis with *Helicobacter pylori* in October 2003

- History of cancer of the colon in a brother and a sister

Lifestyle:

Married, father of a 9-year-old child.
Has lived reclusively for over 3 years without impact on his dietary regime. Deprived of sun exposure since this date.
No smoking or alcohol consumption.
General condition maintained over recent months enabling, according to his friends and family, maintenance of normal and sustained day-to-day activity.

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History of the illness

The information stated here was reported by his personal doctor, Doctor Daka, Professor Hentati, consultant neurologist at the Institute of Neurology / Faculty of Medicine of Tunis, and his family and friends. Some of the biological results reported come from samples sent to the University Hospital of Tunis.

The initial symptoms began on 12 October (D0), 4 hours after the evening meal, with a feeling of faintness with nausea, vomiting and abdominal pain, but no fever. The clinical examination reported by his personal doctor was normal. The digestive symptomatology was secondarily added to with diarrhoea, somewhat aqueous, non-haemorrhagic, non-mucousy, accompanied by frequent feeling of the need to defecate, in a context of deterioration of the general condition with increasing asthenia, loss of appetite and weight loss of 3kg in 2 weeks, still with no fever.

An FBC conducted on 13 October showed a leucocyte level of 12,300/mm³ (75% PN, 5.5% monocytes and 19% lymphocytes), a Hb level of 16.8 g/dl and a platelet level of 177,000/mm³ (75% PN, 5.5% monocytes and 19% lymphocytes), an Hb level of 16.8 g/dl and a platelet level of 177,000/mm³.
The clinical picture persisted in the following days and on 18 October (D+6) thrombopaenia was noted at 72,000/mm³, with no abnormality of the other lines except an Hb level at 18 g/dl (haemoconcentration?). The hepatic assessment found slight cytolysis with no cholestasis. An upper digestive endoscopy was conducted, which showed an appearance of non-specific gastritis; the biopsies conducted did not reach the pathological anatomy laboratory of Tunis. The abdominal/pelvic echography was normal, with in particular the absence of hepatosplenomegaly or adenopathy, with the hepatic echostructure being normal; only the presence of vesicular lithiasis was noted, with no distension on the extra- or intra-hepatic bile ducts.

On 20 October (D+8), the thrombopaenia worsened with a platelet level of 53,000/mm³ and a moderate neutropenia of 920/mm³, which corrected itself secondarily to the benefit of a slight hyperleukocytosis (10,000 to 15,000/mm³) with neutrophils with moderate monocytosis (level varying between 1,500 and 4,000/mm³). The reticulocytosis was low and the schizocytosis was below 0.5%.
A myelogram was conducted on 25 October (D+13), interpreted in Tunis, highlighting bone marrow of normal richness with appearance of moderate myelodysplasia, presence of megakaryocytes (dystrophic?) and an increased number of macrophages presenting aspects of haemocyte phagocytosis.

The infection assessment (blood cultures, CBEU, faecal cultures) was negative and the autoimmunity assessment normal (Faculty of Medicine of Tunis).

On 26 October (D+14), the platelet level fell to 46,000/mm³. The hypothesis of peripheral thrombopaenia of immunologic mechanism was raised, leading to the indication of perfusions of gamma globulins at high doses on 26 October (20 grams) and 27 October (25 grams), which is D+14 and D+15.

The day after the perfusion of immunoglobulins, the onset of attention difficulties was noted (D+13) associated with sleepiness and slowed ideomotor responses (D+14). The detailed neurological examination undertaken by Prof Hentati before, during and after this episode remained normal with no deficit, signs of coning or meningeal syndrome.

Gamma globulins were suspended and corticosteroid therapy begun, in the hypothesis of immunological thrombopaenia and faced with the medullary hemophagocytosis aspect, for which he received 100 mg in two doses 12 hours apart on 27 October (D+15) in the form of methylprednisolone. Alongside these corticosteroids ciprofloxacin and cefotaxime were prescribed as preventative antibiotics.
There was a temporary improvement in the neurological picture the day after the corticosteroid treatment.

The FBC of 28 October highlighted an aggravation of the thrombopaenia with a platelet level of 26,000/mm³, resulting in a platelet transfusion (6 platelet units). The platelet level on the next day, 29 October, the morning of the transfer into France, was 68,000/mm³.

During these two weeks there was a persistence of the digestive problems, such as nausea, vomiting, anorexia, diarrhoea and faecal urgency, always in the context of apyrexia and without biological inflammatory syndrome. The asthenia increased, requiring continual bed confinement.

The patient was transferred into France on 29 October (D+17).

Upon arrival in the haematology department

Arrival on Friday 29 October at 14:30 = D'0

1 – Clinical examination

The vital signs on arrival were as follows: temperature at 36.2º then 36.6º after a few hours, blood pressure 135/85, heart rate 65/min. O2 saturation in ambient air was 100%.

The patient was confined to bed, very asthenic, conscious, presenting an ideomotor retardation, but without real confusional state, a certain degree of disorientation upon arrival fading after a few hours with appropriate behaviour and responses. Absence of meningeal syndrome. The neurological examination was normal, without signs of coning, no impairment of the cranial nerves, the osteotendinous reflexes were absent in the lower limbs and weak in the upper limbs, [condition known for many years (Prof Hentati)], plantar cutaneous reflexes were in flexion, no problem with superficial sensitivity. Walking was possible with help. There was a known postural tremor (treatment with avlocardyl). Examination of the back of the eye was normal.

The skin showed areas of vitiligo depigmentation. There were cutaneous haematomas predominant at the vein puncture points of the forearms, but no spontaneous cutaneous-mucous haemorrhagic syndrome. There were no signs suggesting thrombosis of the large veins of the lower limbs. Similarly there were no cutaneous ischaemic necrosis symptoms.

There were eczema type nasogenian and peribuccal erythemato-squamous lesions. The tongue and the oral cavity showed a slight whitish coating suggesting a candidiasis thrush without mucous lesions elsewhere.

The abdomen was soft, but sensitive to palpation in its entirety, without defence. Hydroaeric noises were present. There was no hepatomegaly, no collateral circulation, no stellate angiomas or clinical ascites. There was no splenomegaly. The various ganglionic areas were free.

There were moderate oedemas of the lower limbs predominant in the ankles with no other sign of right or left cardiac insufficiency. The pleuropulmonary and cardiac examination was normal.

The urine was clear. The patient presented many episodes of faecal urgency or emissions of afaecal liquid stools.

2 – Biological examinations (29/10/04 = D'0)

Haemogram:

The level of leucocytes was 39,000/mm³, including 90% PNN, 6% lymphocytes (2,340/mm³), 4% monocytes (1,560/mm³).

The slide smear shows the presence of a few images of activated lymphocytes and rare images of apoptosis, without immature blastic elements and without myelaemia.

The haemoglobin level was 15.6 g/dl with a MCV of 98 µ3, the level of reticulocytes was 19,311/mm³. Erythrocyte morphology was normal without circulating erythroblastosis, schizocytosis was insignificant at 0.2% and there was no parasitaemia.

Platelet levels were 54,000/mm³ the day after the platelet transfusion (6 units) undertaken in Ramallah.

Haemostasis:

Prothrombin level at 36%, APTT at 71 s for a control of 33 s, fibrinogen level at 0.6 g/l; fall in vitamin K dependent co-factors and factor V (49%), antithrombin level at 17%. Factor VIII was 237%. D-dimers were > 4 µg/ml and FDPs > 20; soluble complexes were negative.

This profile of coagulopathy associated with thrombopaenia was that of a disseminated intravascular coagulation. There was possibly also hepatopathy with insufficient production of procoagulant factors (deficiency of Vitamin K and/or associated hepatocellular insufficiency).

Biochemistry:

Na: 137; K: 3.8; CO2: 25.3; Chlorine 103
Normal renal function (urea: 5.3 mmol/l; creatinine: 75 µmol/l)
Corrected calcium level: 2.26; phosphorus: 0.66; magnesium: 0.78
GOT: 99 (N<60); GPT: 62 (N<60); GT: 99 (N<61); LAP 192 (N<129)

Total bilirubin: 76 (N<17) of which free: 41 and conjugated: 35 (N<5)
LDH 679 (N<440); Haptoglobin < 0.30
Ferritin 1,100 (n<464); Triglycerides: 0.42 (N>0.6)

Amylase: 46 (N<100); Lipase: 33 (N<60)
Hypoproteinaemia at 51.2 g/l of which 24.5 g/l albumin
Protein electrophoresis: polyclonal increase in Ig with presence of beta-gamma block (recent IV-Ig perfusion). Presence of a monoclonal Ig of very low intensity IgG lambda in immunofixation.
β2microglobulin: 1.3 (Normal)

PRC: 8.4 mg/l (N<6)
Procalcitonin < 0.5

Vitamin B12 > 1,000 pg/ml (N: 239-931)
Serum folate: 5.8 (N: 2.76-20)
Free T4: 21.9 pmol/l; Free T3: 6.82 pmol/l; TSH: 0.32 mU/l
Cortisol: 8h: 394 mmol/l (N: 123-626) / 20h: 512 mmol/l (N: 46-389)

Infection tests:

The various samples taken for infection testing were implemented on arrival: haemoculture, uroculture, coproculture, parasitological and virological examination of the stools, myeloculture (BK), serodiagnostics, PCR test (Herpes virus, enterovirus, mycobacteria, etc.)

Coprological analysis:

These were afaecal diarrhoeic stools.
Microscopic examination only found a few erythrocytes and rare polymorphonuclear eosinophils. The bacterial flora was polymorphic upon direct examination with many filamentous types of yeast.

The coproculture highlighted many colonies of *Candida albicans*. The test for the following pathogens was negative: *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Clostridium difficile*. The test for the *C. difficile* antigen and toxin was negative.

Myelogram:

Rich marrow with cellularity scored at 3-4/5
Good representation of all medullary lineages
Presence of 40 megakaryocytes per smear, plateletogens of normal morphology
The granulocyte lineage was present and hyperplasic
The erythroblast lineage was reduced, of normal morphology
Presence of macrophagic cells (1%) with haemophagocytic activity
Absence of infiltration by immature, lymphomatous or extra-haematopoietic cells
Absence of parasitic elements

Medullary immunophenotyping:

Absence of cytometric elements in favour of a B or T cell clonal expansion

Immunohaematological examination:

Coombs' test positive ++ IgG without complement

Tumoral markers:

CEA, AFP, PSA, CA19.9: negative (CEA very slightly raised)

Skull and chest/abdominal/pelvic tomodensitometry examination:

Skull: absence of haemorrhagic or ischaemic process
Thorax: absence of significant images
Abdomen: antropyloric and duodenal parietal thickening with appearance of pseudo detachment of the mucous membrane which was enhanced after injection. Appearance in favour of infectious or inflammatory lesions, not suggesting tumoral infiltrating pathology. Identical more or less diffuse appearance of the colic mucous membrane.
Absence of abnormality of the renal, splenic or hepatopancreatic parenchyma. Absence of adenomegaly.

Cerebral MRI:

Examination normal within the limits of the pictures showing artefacts owing to the patient's movements. In particularly there were no images suggesting haemorrhagic or thrombotic processes in connection with the DIC.

Echocardiograph: Normal

To sum up

Patient aged 75, no obvious history, presenting an alteration to the general condition in a context of gastroenteritis type digestive symptomatology with blood-free diarrhoea, having started suddenly 2 weeks before his arrival in the department.

The primary elements of the additional assessment show a syndrome picture combining:

- An appearance of scannographic inflammatory **enterocolitis** with thickening of the mucous membrane of the whole of the digestive tract without appearance of a tumoral pathology, accompanied by biochemical stigmata of protein-losing enteropathy.

The initial bioclinical summary was discussed at two multidisciplinary meetings bringing together:

- *Professor de Revel, Doctor Fagot, Doctor Souleau, Haematology Department, Hôpital Percy*
- *Doctor Hervé, Doctor Foissaud, Clinical Biology Department, Hôpital Percy*
- *Professor Jeanbourquin, Medical Imaging Department, Hôpital Percy*
- *Professor Algayres, Internal Medicine Department, Hôpital du Val-de-Grâce*
- *Doctor Boyer-Neuman, Haemostasis Laboratory, Hôpital Antoine Béclère*

Initial therapeutic treatment

Pending the return of the various anti-infection samples, treatment was implemented on 29/10/04 combining:

1 – Rehydration with electrolytic, multivitamin and trace element compensation by peripheral venous means, then via a femoral catheter fitted on 30/10/04.

2 – Systemic antibiotic treatment targeting enterobacteria and anaerobic germs: piperacillin/ tazobactam (4g x3) and ciprofloxacin (400mg x2).

3 – Symptomatic treatment of the DIC combining:

- Low-dose heparin (100 UI/kg) due to an imbalance in the procoagulant/coagulation inhibitor balance
- Platelet transfusions for a level <20,000/mm³
- Fresh frozen plasma for a fibrinogen level <0.8 g/l

4 – Corticosteroids at 1 mg/kg were introduced on 30 October (D'+1), then 0.5 mg/kg, faced with the following elements: negativity of the initial infection test (direct and culture), somnolent state suggesting metabolic encephalopathy identical to the initial Ramallah episode (D+17) with a good response to corticosteroids and appearance of macrophage activation with medullary hemophagocytosis.

An adjuvant treatment was added to the corticosteroids from this date: fluconazole (buccal candidiasis and carrying of *Candida albicans* in the stools) and acyclovir (medullary hemophagocytosis pending the viral PCR). The aggravation of the choleostasis (isolated hyperbilirubinaemia) present upon arrival suspended this treatment after 48 hours.

Evolution in the department (29/10/04 to 03/11/04)

1 – Under rehydration, antibiotics and then second course of corticosteroids the general condition of the patient seemed initially to improve somewhat with:

- Improvement to the digestive symptomatology in 48 to 72 hours: reduction in abdominal pain, lower frequency of stools, which became faecal, and the faecal urgency, disappearance of the nausea and vomiting and resumption of light feeding by mouth.

- Improvement to the stuporous condition with resumption of a little activity: walking in the bedroom, sitting in the armchair, appropriate communication with friends and family.

2 – The infection samples proved negative with maintenance of stable apyrexia and absence of inflammatory syndrome.

3 – The DIC remained stable under symptomatic treatment without aggravation or, however, spontaneous improvement. There were no spontaneous cutaneous or mucous haemorrhagic stigmata. There were no clinical elements suggesting thrombotic complications of the activation of coagulation.

4 – The haematological profile remained stable with persistence of the polynucleosis with low CRP and absence of isolation of bacterial germs (possible effect of demargination but present upon arrival before corticosteroid treatment), post-transfusion platelet yield satisfactory. A progressive reduction was noted in the haemoglobin levels without exacerbation of the haemolysis stigmata, with reduction in the LDH levels and absence of significant schizocytosis (haemodilution, repeated blood removal, cytokine inhibition of the erythropoiesis…?).

5 – The disturbances to the hepatic assessment present upon arrival were specified with aggravation of the hyperbilirubinaemia, which increased from 76 µmol/l on 29/10/04 to 218 µmol/l on 02/11/04, predominantly conjugated bilirubin, with furthermore normalisation and stability of the GOTs and LAPs. Furthermore, the levels of LDH and ferritin, moderately high upon arrival, fell at the same time to tend towards values close to normal after a few days. At the same time a slightly high and fluctuating ammoniemia (80 to 200 µmol/l; N<50) should be noted.

6 – The neurological condition deteriorated from 02/11/04 (D'+5) with reappearance of the somnolence then development of confusional state in the night of 02 to 03/11/04. The neurological examination did not show any obvious abnormality other than a temporary anisocoria. A further brain scan was conducted, which was normal.

7 – The next day, 03/11/04, the stuporous condition aggravated without metabolic explanation. The neurological examination (Doctor Berets – neurologist) showed:

- Coma with responses only to nociceptive stimulations with movements of the lower limbs and grimaces. Anisocoria (poorly reactive left meiosis, intermediate right pupil poorly reactive), doubt over a left VI, pendulum movement of the eyes. No spontaneous movement of the upper limbs, hypertonia in flexion of the two upper limbs. Spontaneous movements of the lower limbs, bilateral Babinski sign, abolition of the osteotendinous reflexes of the 4 limbs.

- An EEG was carried out which showed a diffuse retardation of cerebral activity with slow waves and no signs of focusing.

The diagnostic hypotheses of this comatose evolution were at this stage of the discussion:

- metabolic (cause?)
- infectious
- vascular haemorrhagic or thrombotic (DIC)

The patient was transferred to the intensive care department (Prof Pats, Prof Perez) for treatment of the coma and additional investigations.

Conclusion

Patient aged 75 hospitalised for enteropathy, suggesting infectious enterocolitis evolving for two weeks associated with severe disseminated intravascular coagulation, no infectious etiology identified at the stage of transfer to intensive care, and an isolated medullary hemophagocytosis.

Improvement to the general and digestive clinical symptomatology under symptomatic treatment and parenteral antibiotic treatment.

Progressive hepatopathy with cholestasis without cytolysis.

Fluctuating encephalopathy type neurological problems the aggravation of which towards a comatose condition necessitated the transfer to intensive care on 03 November 2004, the sixth day of his admission to the haematology department.

Written in Clamart, 14/11/04

Professor Thierry de Revel
Head of the Haematology Department

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